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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/613,177
Filing Date: July 10, 2000
Appellant(s): SAMPATH ET AL.

Ignacio Perez de la Cruz
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 1, 2005 appealing from the Office action mailed November 19, 2004.

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(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

None.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The 35 U.S.C. 103 rejection over Harris in view of Smart and further in view of Ozkaynak is withdrawn in view of Appellant's arguments. This renders claim 48 as also only objected to, but otherwise allowable.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,083,690	HARRIS	7-2000
5,650,276	SMART	7-1997
WO 94/18239	NADAL-GINARD	8-1994

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6, 9, 13, 36, 43-47, 49 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al (U.S. Patent 6,083,690) in view of Smart et al (U.S. Patent 5,650,276) and further in view of Nadal-Ginard (WO 94/18239).

Harris teaches a method for identifying a compound that induces a BMP mediated biological effect (see column 51, claim 8 and column 4, lines 20-31, for example) comprising:

(a) providing a test cell comprising a DNA (see column 51, claims 5 and 6 and column 12, example 3) comprising:

(i) a transcription activating element responsive to said morphogen (see column 51, claim 1 and column 4, line 55 to column 5, line 35, where Harris expressly contemplates the use of promoters from genes including BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, as well as similar genes as shown by column 5, line 33)

(ii) a reporter gene encoding a detectable gene product, the transcription activation element being in operative connection with the reporter gene (see column 51, claim 6 and claim 8 and column 4, line 63 to column 5, line 8, where the promoter from the morphogen responsive gene is operatively linked to reporter genes such as firefly luciferase, CAT or green fluorescent protein),

wherein the reporter gene is transcribed when the DNA is present in a cell that is

(1) responsive to the morphogen and (see column 51, claims 1-8 and column 5, lines 37-50, where Harris uses cells such as osteoblasts)

(2) contacted with said morphogen (see column 51, claim 8, where Harris expressly teaches screening for osteogenic agents).

(b) exposing the test cell to a candidate compound (see column 51, claim 8 and column 12, example 3).

(c) detecting expression of said detectable gene product (see column 51, claim 8 and column 12, example 3),

wherein an increase in expression of the detectable gene product after exposing the test cell to the candidate compound indicates that the ability of the compound to induce morphogen mediated biological effects wherein said morphogen-mediated biological effect requires the presence of said morphogen-responsive transcription activating element so as to thereby identify a compound that induces a biological effect mediated by a morphogen (see column 13, example 4, lines 15-25, where Harris shows that compounds which enhance expression have the ability to induce morphogen mediated biological effects.)

With regard to claim 13, Harris teaches synthesis of compounds (such as recombinant BMP-2) which induce morphogenic effects (see column 13, example 4).

With regard to claim 36, Harris teaches the screening method as described above and teaches detecting the DNA binding within "approximately" 2 hours (specifically somewhat more than 10 minutes as shown in column 12, lines 60-67, which meets the "approximately" 2 hour requirement given the broad scope of "approximately" 2 hours).

With regard to claim 45, Harris teaches the use of promoters from BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, as well as similar genes as shown by column 5, line 33.

With regard to claim 46, Harris teaches the use of human promoters (see column 6, lines 61-67).

With regard to claims 47 and 49, Harris teaches that the biological effect may include enhancing bone nodule formation (see column 13, example 4).

With regard to claim 50, Harris teaches that osteocalcin expression may be enhanced (see column 13, example 4).

While Harris expressly recognizes that the promoters from other, similar, genes can be used in the screening method, Harris does not specifically teach the use of the OP-1 gene.

Smart teaches a screening method wherein "The invention features a method of screening candidate compounds for the ability to modulate the effective local or systemic concentration or level of morphogenic protein in an organism. (see column 2, lines 61-64)." Smart teaches the desirability of screening candidate compounds for their ability to modulate morphogenic proteins (abstract). Smart expressly teaches OP-1 and OP-2 derived from humans (see column 4, line 38). Smart teaches morphogenic effects such as stimulating proliferation of progenitor cells (See column 2, lines 26-59) including osteoblasts (see column 17, lines 35-36).

Harris in view of Smart teach the limitations of claims as discussed above. Smart expressly teaches that OP-1 is associated with cells in the muscle (see column 16, lines 31-33).

Harris in view of Smart do not teach the use of the MEF-2 or AP-1 elements, which are functional in muscle cells.

Nadal-Ginard teaches screening for agents which either enhance of decrease the interaction of MEF2 transcription factors as well as MyoD and MASH transcription factors (abstract).

Further, the sequences of Harris, Smart or Nadal-Ginard are all "variants" of the nucleotides disclosed in claim 30 and meet this limitation.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to apply the method of Harris, who specifically suggests the use of other promoters, to the screening of other compounds which induce morphogensis since Smart expressly notes the desirability of screening compounds for their ability to modulate morphogenesis (see column 2, lines 61-64, abstract, column 15, lines 55-64, especially). So an ordinary practitioner, faced with the teaching of Harris that other promoters are of interest, would have been expressly motivated by Smart to study OP-1, which is shown by Smart as an important morphogenic protein. Smart teaches that it is desirable to screen compounds for the physiologic effect of morphogenesis. That is, an ordinary practitioner interested in determining which compounds would effect the physiologic pathway termed morphogenesis as motivated by Smart would have been motivated to apply the method of Harris to this analysis since Harris expressly suggests analysis of such pathways and since Harris clearly indicates that such screening can result in clinical and therapeutic advantages (see example 4).

Further, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to apply the method of Harris in view of Smart to the downstream screening of MEF2 related compounds for the study of differentiated tissue as taught by Nadal-Ginard since Nadal-Ginard states "The agents useful in the invention either enhance or decrease the interaction between a pocket protein, eg retinoblastoma protein and a tissue specific trasncription factor, eg members of the MyoD, MEF2 or MASH family of transcription factors" (abstract)." Nadal-Ginard further notes that "Applicant's discovery provides the basis for screening therapeutic agents useful for regulating the switch between the cell's growth phase and a terminally differentiated state (page 4, lines 18-20)". Thus, an ordinary practitioner would have been motivated by Nadal-Ginard to screen for compounds which are involved in differentiation using the MEF2 transcription factor sites in view of Nadal-Ginard's express motivation to use these enzymes in screening between differentiation and growth.

(10) Response to Argument

Introduction

The claimed invention is drawn to a screening method to identify compounds that induce "morphogen-mediated biological effects" by screening test cells for reporter gene activation based upon activation of a transcription activating element. The prior art of Harris teaches, as discussed in the rejection above, methods of screening for compounds using the same method elements as claim 1, except for the use of a "transcription activating element that is responsive to, and distinct from the gene

encoding said morphogen." The question before the Board of Patent Appeals and Interferences in this case is what does that limitation mean, and does the prior art teach and suggest the limitation in the context of the compound screening method.

In addressing the interpretation of the phrase "transcription activating element that is responsive to, and distinct from the gene encoding said morphogen", the initial source of guidance must be the specification. The specification discusses the claimed invention at pages 20-24, and specifically notes "The present test cell is any cell comprising DNA defining an OP-1 responsive transcription activating element operatively associated with a reporter gene encoding a detectable gene product (see page 20, lines 23-25 of the specification"). The transcription activating element of the claim is therefore any element which is responsive to OP-1 (or one of the other claimed elements), so long as that element is distinct from the specific gene. At pages 25 and 26 of the specification, the specification details the fact that the preferred embodiment of the response element are sequences derived from the native the mouse type X collagen gene. Therefore, in interpreting this claim, any transcription activating element that is not the element of the morphogen at issue will meet the limitation of the claim.

All Elements are Taught by Prior Art

Harris, Smart and Nadal-Ginard teach all of the claimed invention. In particular, as discussed in the rejection, Harris teaches all of the elements of claim 1 except for the use of a transcription activating element that is distinct from the gene encoding the morphogen. Smart teaches screening OP-1 and the other morphogens absent from Harris.

Nadal-Ginard teaches the final element, the use of a transcription activating element that is distinct from the gene encoding the morphogen. Specifically, Nadal-Ginard teaches the concept of screening for reporter gene activation by using a transcription activating element that is distinct from the gene of interest. Nadal-Ginard shows at pages 9 and 10 a method in which a cis-acting sequence is linked to a reporter gene, and then at page 9, line 26, "The ability of the candidate agent to decrease cell proliferation is therefore indicated in this assay by an increase in the level of reporter gene expression, which is in turn a function of the ability of a pocket protein-transcription factor complex to bind the regulatory sequences upstream of the reporter gene." Nadal-Ginard expressly teaches the use of a transcription activating element that is distinct from the "pocket protein" which binds to the transcription factor, in a screening assay. Nadal-Ginard further teach the specific interaction of proteins such as the retinoblastoma protein (Rb) with the transcription factor MEF-2 (see abstract). Nadal-Ginard recognizes the specific advantage of use transcription activating elements that are distinct from the gene of interest, noting that "Without binding to the pocket protein, tissue-specific transcription factors are not able to turn on or enhance transcription of tissue-specific genes. Similarly, without binding to the cellular factor, a pocket protein is unable to induce growth arrest (see page 4, lines 9-14)."

Therefore, Nadal-Ginard expressly teaches the element that is argued to be absent. Nadal-Ginard teaches screening a cell where the reporter gene is linked to a transcription activing element that is responsive to a transcription factor, but where the element is distinct from the candidate agent (here a pocket protein) that is being

screened.

Definition of Morphogen

Appellant argues that Nadal-Ginard never teaches the screening of morphogens. The specification defines a morphogen at page 14.

> Morphogens, as defined herein, induce or re-induce mammalian cells, particularly uncommitted progenitor cells, to undergo a fully integrated developmental cascade of
> biological and molecular events that culminate in the morphogenesis of fully differentiated, functional tissue of a type appropriate to the context or local biological environment in
> which morphogenesis is induced, including any vascularization, connective tissue formation, enervation and the like characteristic of tissue naturally-occurring in such a context.

This definition clearly indicates that a morphogen is a compound which can induce cells to move from an undifferentiated state to a differentiated state. This is consistent with the express teaching of Nadal-Ginard, who is interested in screening for compounds which regulate "the switch between the cell's growth phase and a terminally differentiated state (see page 4, lines 20-24)." Therefore, Nadal-Ginard expressly teaches screening for compounds which are morphogens, at least in so far as Appellant's specification defines morphogens. The fact that Nadal-Ginard does not use the word "morphogen" does not detract from the teaching of the reference. It is not a requirement that the prior art use ipsis verbis in suggesting the claimed invention, only that the prior art teach the invention.

When Appellant argues that Nadal-Ginard does not teach DNA elements responsive to the growth phase of the cell, this is incorrect. Nadal-Ginard expressly

teaches the use of MEF-2 elements (see abstract) which claim 2 of Appellant's evidences are morphogen responsive. Finally, Claim 14 of Nadal-Ginard expressly teaches screening for factors involved in terminal differentiation.

Motivation

There is express motivation to combine the references in this case. Harris teaches screening morphogens in the specific Markush group as well as all of the other elements of the claim except that Harris does not teach the use of transcriptional activating elements distinct from the gene encoding the morphogen. Nadal-Ginard does not teach the specific morphogens listed in the claim, but teaches a morphogen screening method which requires the use of transcriptional activating elements distinct from the gene encoding the morphogen. Nadal-Ginard motivates the use of such distinct elements in order to identify agents that enhance the interaction between the transcription factor and other cellular factors involved in transcription in order to permit identification of therapeutic agents.

Nadal-Ginard applied the finding regarding the interaction of pocket proteins and transcription factors to expressly provide a motivation to perform the screening method, noting "Applicants' discovery provides the basis for screening therapeutic agents useful for regulating the switch between the cell's growth phase and a terminally differentiated state. This provides long awaited advantages in two areas. The first advantage is to identify agents that enhance the interaction between a pocket protein and a transcription factor (see page 4, lines 18-24)."

Therefore, the ordinary practitioner was taught by Nadal-Ginard that transcription

activating elements distinct from the gene of interest could be used in screening for therapeutic agents, and Nadal-Ginard motivates such a use in order to identify interactions with the transcription factor and permitting identification of compounds which regulate the switch between the cell's growth phase and terminally differentiated state, or morphogens in the vernacular of the specification (see page 14, lines 5-16 of the specification). In combination with the teaching of Harris that the BMP proteins (and the teaching of Smart that the OP-1 protein) are proteins of interest for screening for therapeutic agents associated with regulation of cell growth and differentiation, Nadal-Ginard teaches identification of agents where the transcription activating element is responsive to, but distinct from the gene encoding the morphogen, where the morphogen may be a BMP protein or OP-1.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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